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Serum concentration of Artemisinin after single and chronic oral dose administration in broiler chickens

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Keywords

Artemisinin, serum level, broiler chickens, HPLC

Abstract

Although preliminary studies have shown the anticoccidial effects of Artemisinin in broiler chickens, there are no proofs of its pharmacokinetics. The objective of this study was to determine the serum concentration of Artemisinin after single and multiple oral administration in broiler chickens. A total of 390 one-day-old healthy Ross 308 chickens were divided randomly into two groups. In the first group, single oral doses of 0, 1, 5, 25, 125, 250, 500 and 1000 mg/kg Artemisinin were given on day 44, and in the second group 0, 17, 34, 68 and 136 ppm of Artemisinin were given chronically in the diet over a 36-day period. An HPLC system with UV detector was used to determine serum level of Artemisinin. Data were presented as Mean ± SE and analyzed using the linear mixed model ($p < 0.05$). The results showed that in both groups the serum levels of Artemisinin were generally very low and there were no significant differences between multiple and single dose administration groups or between different doses in each group ($p < 0.05$). The serum levels of Artemisinin in the chickens that had received single doses were in the range of 25.38 ± 0.15 to 42.27 ± 12.04 ng/ml and 24.68 ± 0.12 to 29.24 ± 1.72 ng/ml for those that had received chronic doses. It can be concluded that serum level of Artemisinin administered orally to the chickens as single or chronic doses is low which seems to be due to low oral absorption and metabolism induction and thus, can have high therapeutic index and good anticoccidial properties.

Abbreviations

HPLC: High Performance Liquid Chromatography
A. annua: *Artemisia annua*
OPG: Oocyst Per Gram (of feces)
A. sieberi: *Artemisia sieberi*
SEM: Standard Error of the Mean
AUC: Area Under the Curve
SD: Standard Deviation
RSD: Relative Standard Deviation

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Introduction

Artemisia annua (*A. annua*) or Qinghao has been used as a traditional remedy for more than 2000 years for treatment of skin bugs, itchy scabs, intestinal helminthes and diarrhea. It has also been used as an antipyretic, astringent, sedative and anti-malarial agent (Zhu, 1987, Meshnick et al.,1989, Woodrow et al., 2005, Weinberg and Moon, 2009). Artemisinin, the active ingredient of *A. annua*, is now used as a powerful medicinal product with excellent efficacy, rapid action and a high safety profile in combination-therapy against multidrug-resistant species of *Plasmodium falciparum* in the endemic regions of malaria (Olliarioand Taylor, 2004, Willcoxet al., 2007, Weinberg and Moon, 2009). Further studies have revealed that both *A. anuua* extract and Artemisinin can be effective against protozoan infections including avian coccidiosis, which is the most important parasitic disease in the poultry industry (Oh et al.,1995a, b, Allen et al., 1997, Allen and Fetterer, 2000; Zhang and Zeng, 2005, Arab et al., 2006 & 2012, Dallouland Lillehoj, 2006, Brisibe et al., 2008, Naidoo et al ., 2008, Kaboutari et al., 2014, and Pirali et al., 2014). In the 1990s, the anticoccidial effect of *A. annua* extract, its dried leaves and pure Artemisininon the broiler coccidiosis was reported (Oh et al., 1995a, b, Allen et al., 1997). It has been shown that Artemisinincan reduces OPG output and improves animal performance with low doses (1 & 2.5 mg/kg) in the chickens challenged with Eimeria species (Arabet al., 2006). Later it was reported that prophylactic and therapeutic administration of granulated extract of A. sieberi reduced OPG output, lesion score, bloody diarrhea and mortality rate in experimental coccidiosis (Arab et al., 2012, Kaboutari et al., 2014, Pirali et al., 2014). Primary toxicological studies indicated that Artemisinin is highly safe at high doses. Its administration at 2500 times of therapeutic doses was associated with only some mild pathological signs in the kidney, liver and nervous system (Arab et al., 2009). Because of the increasing resistance to conventional anticoccidial drugs, herbal products including Artemisinin offer a potential alternative to control coccidiosis in chickens (Allen and Fetterer, 2000, Arab et al., 2006, Kaboutari et al., 2014, and Pirali et al ., 2014). However, there is no information available about the toxico-pharmacokinetic parameters of Artemisinin in chickens. It is not clear whether low toxicity of Artemisinin is due to its low oral absorption and subsequently low blood and tissue concentration or due to its high safety and therapeutic index. Therefore, this study was conducted to determine the serum concentration of Artemisinin following oral administration in single and multiple doses in broiler chickens.

Materials and Methods

Animals and experimental groups

A total of 390 one-day-old Ross broiler chickens were obtained from a commercial hatchery and were housed under standard conditions in metal cages. The chickens were vaccinated against Bronchitis, Newcastle and Bursal diseases and had access to feed and water ad libitum. They were divided randomly into two groups on day 8. The chickens in group one received a single dose of 0, 1, 5, 25, 125, 250, 500 &1000 mg/kg Artemisinin in 2 ml solution on day 44. In the second group (multiple treated group) 0, 17, 34, 68 & 136 ppm of Artemisinin was administered in the diet from day 8 to day 44. All experiments were done in accordance with the principles of the NIH guidelines for care and use of laboratory animals and approved by the ethical committee of the University of Shahrekord.

Artemisinin administration

Artemisinin powder (99% purity) was obtained (from Sichuan Arts and Crafts Import and Export Corporation, China), dissolved in ethanol and diluted by an appropriate volume of distilled water, in order to obtain the maximum concentration of alcohol not to exceed 10% of the solution. The Artemisinin solution that was prepared for multiple administration was sprayed on the diet and mixed completely (each time, 5 kg of feed for each group) while the single dose preparations were administered by the gavage method.

Blood sample taking and preparation

Blood samples (2 ml) were taken from wing vein of each bird; in the single treated group 1 hour after oral administration of Artemisinin, and in the multiple treated groups at the end of day 44. Blood samples were immediately centrifuged (7000 RPM, 10 min), the sera were collected and Artemisinin extraction was performed (Rawa-Adkonis et al., 2003). Briefly, serum was thawed and dissolved in 5ml of methanol containing 10% HCl. The solution was sonicated for 1.5 min in 3 cycles, and then centrifuged for 10 min, while the supernatant was collected and dissolved in 5ml of petroleum ether. It was then extracted and dried in a rotary evaporator at 400°C. The collected residue was dissolved in ethanol and hydrolyzed by NaOH. The prepared samples were filtered and stored at -20°C until further analysis.

HPLC system

The HPLC system consisted of a Knauer 1001 HPLC pump (Knauer, Germany), a nh-2600 UV detector, a 10 cm × 4 mm Nucleosil C18 column and an auto sampler. The mobile phase was prepared from 20 mmol/L phosphate buffer (K_2HPO_4 & KH_2PO_4, Sigma-Aldrich, USA) and methanol (60:40, Merck, Germany) adjusted at pH 7.9. The volume of the sample that was automatically injected into the loop of the pump was 100 µL at a flow rate of 1.5 ml/min (Liersch et al., 1986, Arab et al., 2006).

Statistical analysis

Data were expressed as mean ± SE that were obtained from at least 3 (for method validation) to 5 samples (for

Table 1
Area Under Curve (AUC) for calibration of serum concentration of Artemisinin

Concentration (ng)	AUC
0	0
1	120401
5	625021
10	1285304
25	3459819
50	638725
100	12542768
200	24955833

each dose). Linear mixed model test was used for analysis and comparison of two main groups as well as different doses in each group. ($p < 0.05$).

Results

Method validation

The HPLC procedure was validated for selectivity, precision, linearity and accuracy according to the guidelines on validation of analytical methods (shah et al.,1991, Guidance for Industry bioanalytical Method Validation, 2001).The linearity of the method was obtained by plotting a calibration curve of peak area against concentration.The calibration curves were constructed using linear regression analysis based on the area under curve (AUC) of the peak and different concentrations of standard Artemisinin ranging from 0.1 to 200 ng/ml (Fig. 1). Table 1 shows the AUC obtained from different concentrations of standard Artemisinin and the calibration curve obtained by plotting these values. The limit of detection was determined as 3 times the ratio of the Standard Deviation (SD) to the slope of the calibration curve that was 0.2 ng/mL, while the limit of quantification was 1 ng/ml. Intra-day precision was determined by analysis of three series of working solutions of Artemisinin with concentrations of 1, 100 and 500 ng/ml. The Relative Standard Deviation (RSD) for all three applied concentrationswas less than 2.7%, indicating that the analysis procedure was highly precise and reproducible for routine analysis. The retention time was 4.6 min and relative extraction recoveries obtained from serum samplesranged from 76.4% to 103.98%.

Serum concentration of Artemisinin

Representative chromatograms obtained from (a) a standard solution of Artemisinin, (b) serum of a chicken that received Artemisinin and (c) that of a blank sample are shown in Figure 2. Serum levels of Artemisinin in chickens that received single or chronic doses of Artemisinin are summarized in Table 2. The level of Artemisinin detected in the serum of both groups was very low (Table 2). In the group which different multiple doses of artemisinin were administered, serum concentration was ranging from 24.68 ± 0.12 to 29.24 ± 1.72 ng/ml, while in the case of those chickens that received single doses of artemisnisin, the serum concentrations were in the range of 25.38 ± 0.15 to 42.27 ± 12.04 ng/ml. The highest concentration was 42.74 ± 0.88 ng/ml obtained from a single dose of 1 mg/kg of Artemisinin, while the lowest concentration of 24.68 ± 0.12 ng/ml was obtained from multiple administrations of 34 ppm of Artemisinin. Statistical analysis showed that there was not any significant differences between the single administration and the chronic administration groups. In addition no significant difference was observed between the group that received multiple administration of dose or the group that received a single administration of dose of Artemisininin in each group.

Discussion

In recent years, Artemisinin has been proposed as an effective candidate against avian coccidiosis, but there is no report about its pharmacokinetics in chickens. To our knowledge, this is the first study specifically designed to determine the serum concentration of Artemisinin following oral administration as single and multiple doses in broiler chickens reporting that the serum concentration of Artemisinin was very low even at high doses and it was not dose dependent.

The HPLC method that was used in this study in order to detect the serum Artemisinin levels is the most accurate, reliable, and preferred method for determination of Artemisinin and its derivatives in biological materials (Arab et al., 2006, Xing et al., 2006, Gu et al., 2008, and Huang et al., 2009). Validation of the method showed that the analysis was precise for Artemisinin determination in serum. Chromatographs were free of interferences and all analysis peaks were at the baseline and Artemisinin was quantified at very low concentrations. Artemisinin and its derivatives have time dependent pharmacokinetics. They have rapid but poor and incomplete oral absorption and low oral bioavailability because of intensive first pass metabolism (Ashton et al., 1998a, b, c, Svensson et al., 1998, Gordi et al., 2002 & 2005a, b, Asimus and Gordi 2006, Golenser et al., 2006). Decreasing serum concentration of Artemisinin and its derivatives following multiple oral administrations has been shown in malaria. There is evidence that Artemisininis a potent and rapid inducer of its own hepatic metabolism in healthy and malaria patients which can decrease its bioavailability. The onset of auto-induction is so fast and the lag time for auto-induction has been reported to be from 0.74 to 1.9 hours (Svensson et al., 1998, Simonsson et al., 2003, Gordi et al., 2005a, b, Asimus et al., 2007). It seems that a single dose of Artemisinin can affect pharmacokinetics of the next dose even one week later. Following

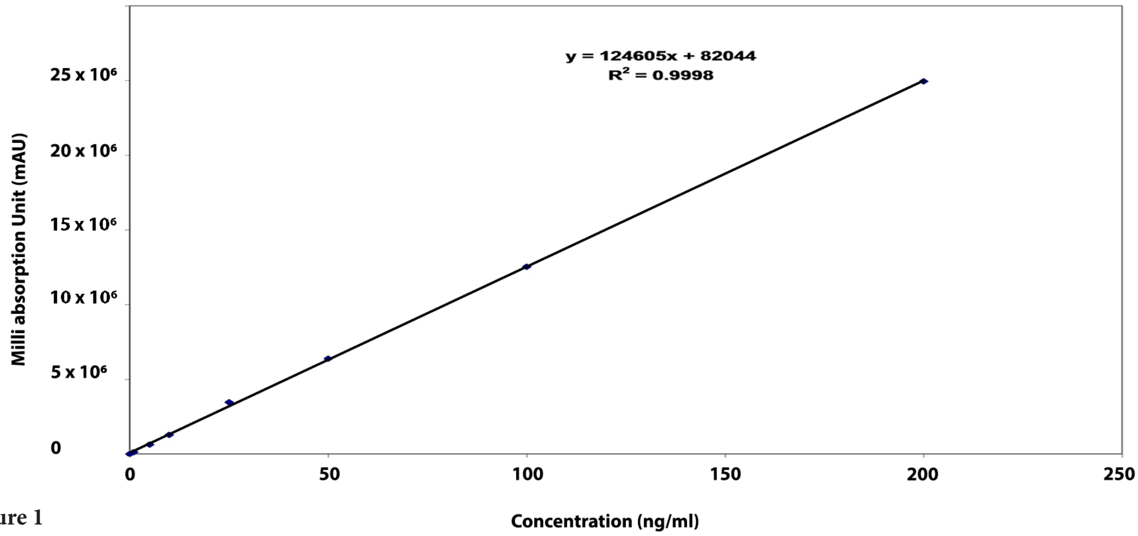


Figure 1
Artemisinin calibration curve in the serum

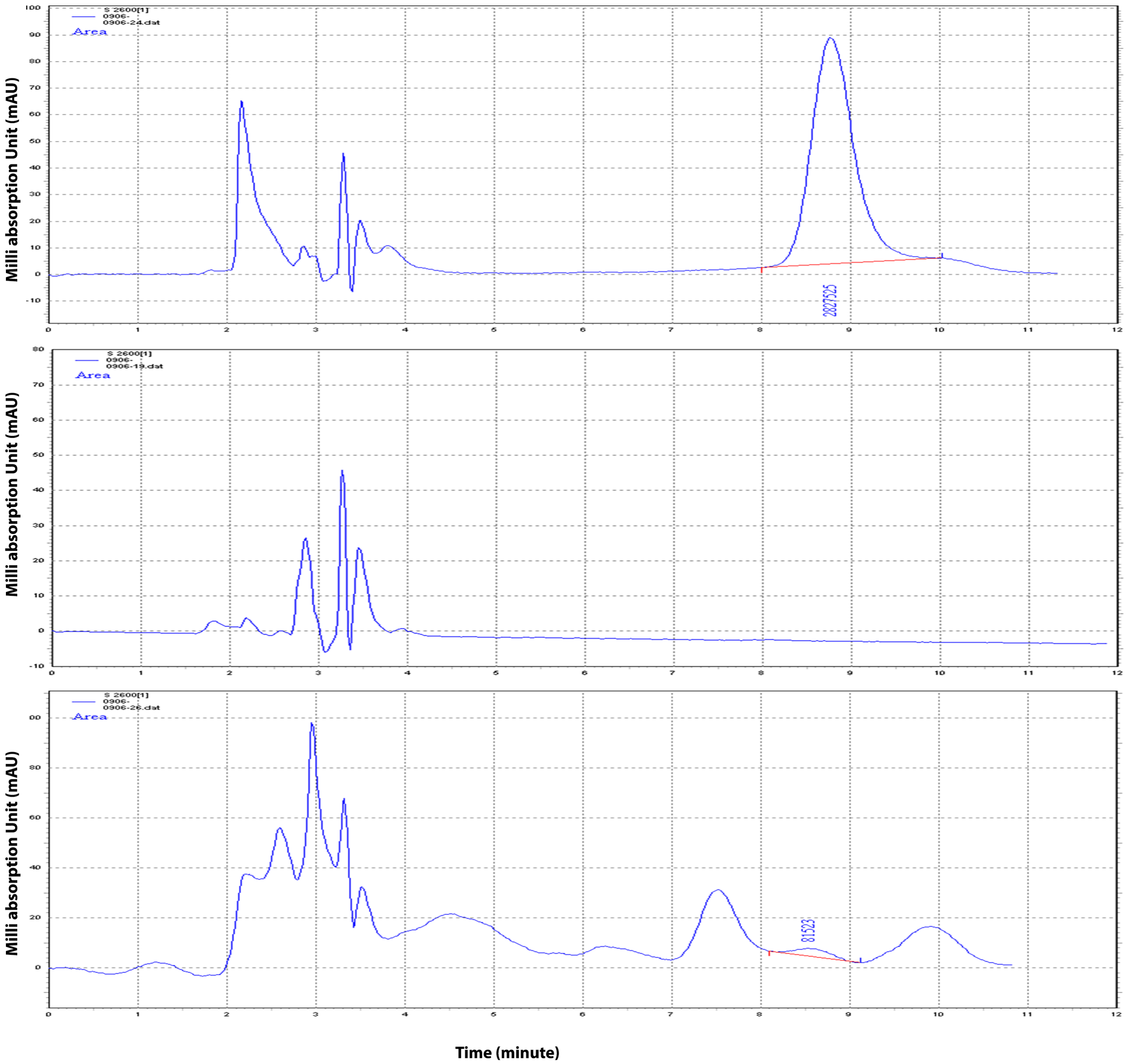


Figure 2
Representative chromatograms obtained from (a) a standard solution of Artemisinin , (b) serum of a chicken that received Artemisinin and (c) a blank sample.

Table 2
The level of Artemisinin (ng/ml) in the serum of chickens exposed to different doses of Artemisinin as single or chronic oral administration.

Dose of Artemisinin	Route of administration	Serum concentration (Mean ± SE)
1 mg/kg	Single dose	42.74864 ± 0.8832 [a]
5 mg/kg	Single dose	25.3804 ± 0.153 [a]
25 mg/kg	Single dose	42.2793 ± 12.0474 [a]
125 mg/kg	Single dose	25.40354 ± 0.1611 [a]
250 mg/kg	Single dose	27.72442 ± 0.8124 [a]
500 mg/kg	Single dose	31.78206 ± 4.6625 [a]
1000 mg/kg	Single dose	27.69964 ± 1.2403 [a]
17 ppm	Chronic dose	27.1616 ± 0.5485 [a]
34 ppm	Chronic dose	24.68744 ± 0.1299 [a]
68 ppm	Chronic dose	29.24714 ± 1.7288 [a]
136 ppm	Chronic dose	26.09498 ± 0.3085 [a]

Similar letters indicate no significant differences between groups

oral administration, hepatic concentration of Artemisinin is the main determinant of the hepatic enzyme induction, and because of the saturable nature of the enzymes involved in first pass metabolism, the auto-induction metabolism is dose dependent. Therefore, the auto-induction will be increased by increasing the dose of Artemisinin (Ashton et al., 1998a, b, c, Asimus et al.,2006 & 2007, Huang et al., 2009). It seems that multiple oral administration of Artemisinin had provided enough time for progressive induction of hepatic metabolism leading to low serum concentration of Artemisinin due to the low oral absorption and also potent induction of hepatic metabolism. Considering the higher metabolic rate of chickens compared to mammals (Gregory, 2002), substantial hepatic first pass effect and metabolism induction may lead to a profound decease in the serum concentration of Artemisinin following multiple oral administration in chickens. Similar to the multiple administration pattern, single oral administration has also resulted in low serum levels of Artemisinin, withno significant difference between these two different cases. The amount of Artemisinin used in a single dose administrations was higher than that of multiple doses. Thus, it seems that in addition to the first pass effects and hepatic metabolism induction, poor and incomplete absorption can also be effective in decreasing bioavailability and subsequently low serum level of Artemisinin.

Human and animal toxicological studies indicated very high therapeutic index and low toxicity of Artemisinin even at high therapeutic and toxic doses (China Cooperation Research Group 1982, Arab et al., 2009, Shahbazfar et al., 2011). It seems that low absorption and bioavailability may be an important reason for the high therapeutic index of Artemisinin. It also decreases tissues concentration and subsequently it decreases the likelihood of drug residue in edible tissues.

Artemisnin exerts anti coccidial effects at very low doses (Arab et al., 2006 & 2012, Kaboutari et al., 2014, Pirali et al., 2014). This study showed that is makes a very low serum concentration. Therefore according to these findings and pathogenesis of coccidiosis that mainly involves the intestinal tract, it seems that local concentration of Artemisinin in the intestinal tract can be more important than its serum concentration for anti coccidial effects. Therefore, low serum concentration of Artemisinin is not only atherapeutic drawback (Titulaer et al., 1991, WongandYuen, 2001), but it can also be considered as an advantage since it makes more intestinal concentration and increases the parasite exposure to a higher intestinal concentration of Artemisinin which enhances its anticoccidial property.

Conclusion

HPLC analysis showed very low serum concentration of artemisinin in the sera of chickens following single and multiple oral administration. This may be due to the low oral absorption, hepatic first pass effect or the potent auto-induction of hepatic metabolism of this drug, which can be a key point in the proper anticoccidial effects and the low toxicity of Artemisinin.

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سطح سرمی آرتمیزینین درجوجه‌های گوشتی به دنبال تجویز خوراکی دوزهای تکی و مزمن

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چکیده

هرچند پژوهش‌های ابتدایی اثر مناسب ضدکوکسیدیوزی آرتمیزینین را در جوجه‌های گوشتی نشان داده اند، اما اطلاعاتی در مورد فارماکوکینتیک آن وجود ندارد. هدف از این پژوهش سنجش غلظت سرمی آرتمیزینین به دنبال تجویز خوراکی تک دوز و دوزهای چندگانه در جوجه‌های گوشتی بوده است. ۳۹۰ جوجه گوشتی یک روزه نژاد راس ۳۰۸ به صورت تصادفی به دو گروه تقسیم شدند. در گروه اول تک دوزهای خوراکی ۰، ۱، ۵، ۲۵، ۱۲۵، ۲۵۰، ۵۰۰ و ۱۰۰۰ میلی‌گرم/کیلوگرم آرتمیزینین در روز ۴۴ تجویز شد. در گروه دوم ۰، ۱۷، ۳۴، ۶۸ و ۱۳۶ ppm آرتمیزینین همراه غذا در یک دوره ۳۶ روزه تجویز می‌شد. از سامانه HPLC با ردیاب فرابنفش برای سنجش سرمی آرتمیزینین استفاده شد. داده‌ها به صورت Mean ± SE نمایش داده شده، با استفاده از آزمون Linear mixed model مورد بررسی آماری قرار گرفتند ($p < 0.05$). نتایج نشان داد غلظت سرمی آرتمیزینین در هر دو گروه بسیار پایین بود و هیچ تفاوتی بین دو گروه تجویز دوزهای چندگانه و تک‌دوز و نیز بین دوزهای گوناگون در هر گروه وجود نداشته است ($p > 0.05$). سطح سرمی آرتمیزینین در گروه دریافت کننده تک‌دوزهای خوراکی در دامنه ۰/۱۵۳۳ ± ۲۵/۳۸۰۴ تا ۱۲/۰۴۷۴ ± ۲۷۹۳ /۴۲ نانوگرم/میلی‌لیتر سرم و در گروه دوزهای چندگانه ۰/۱۲۹۹ ± ۲۴/۶۸۷۷۴ تا ۱/۷۲۸۸ ± ۲۹/۲۴۷۱۷ نانوگرم/میلی‌لیتر سرم بوده است. می توان چنین گفت که سطح سرمی آرتمیزینین تجویز شده به صورت تک‌دوز یا دوزهای چندگانه خوراکی بسیار پایین است که شاید ناشی از جذب و زیست فراهمی اندک خوراکی و القاء متابولیسم کبدی باشد و نقش کلیدی در شاخص بالای درمانی و ویژگی مناسب ضدکوکسیدیوزی دارد.

واژگان کلیدی: آرتمیزینین، سطح سرمی، جوجه‌های گوشتی، HPLC